We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

1

Vitamin D and Cancer

Khanh vinh quốc Lương and Lan Thị Hòang Nguyễn
Vietnamese American Medical Research Foundation, United States

1. Introduction

Vitamin D has been known as a regulator of bone and mineral metabolism by regulation of calcium absorption in the gut and reabsorption by the kidney, which is mediated by the vitamin D receptor (*VDR*). The expression of *VDR* in a variety of cell lines coupled with increased evidence of *VDR* involvement in cell differentiation and inhibition of cellular proliferation suggests that vitamin D plays a role in many diseases. A meta-analysis of randomized controlled trials demonstrated that intake of vitamin D supplements was associated with a significant 7% reduction in mortality from any causes (Autier & Gandini, 2007). A serum 25-hydroxyvitamin D_3 ($25OHD_3$) concentration of 25 nmol/l was associated with a 17% reduction in incidence of cancer, a 29% reduction in total cancer mortality, and a 45% reduction in digestive system cancer mortality (Giovannucci et al., 2006). A low serum $25OHD_3$ was prospectively associated with an increased risk of fatal cancer in patients referred to coronary angiography (Pilz et al., 2008).

Alphacalcidol, a vitamin D analogue, has been demonstrated significant antitumor activity in patients with low-grade non-Hodgkin's lymphoma of the follicular, small-cleaved cell type (Raina et al., 1991). In patient with parathyroid cancer, vitamin D has been shown to avert or delay the progression of recurrence (Palmieri-Sevier et al., 1993). In locally advanced or cutaneous metastatic breast cancer, topical calcipotriol treatment reduced in the diameter of treated lesions that contained *VDR* (Bower et al., 1991). In a clinical trial, high-dose calcitriol decreased Prostatic-specific antigen (PSA) levels by 50% and reduced thrombosis in prostate cancer patients (Beer et al., 2003 & 2006). In hepatocellular carcinoma, calcitriol and its analogs have been reported to reduce tumor volume, increase apoptosis of hepatocarcinoma cells by 21.4%, and transient stabilization of the serum alpha-fetoprotein levels (Dalhoff et al., 2003; Luo et al., 2004; Morris et al., 2002).

Calcitriol additively or synergistically potentiates the antitumor of other types of chemotherapeutic agents. Calcitriol enhances cellular sensitivity of human colon cancer cells to 5-fluorouracil (Liu et al., 2010). Combination of calcitriol and cytarabine prolonged remission in elderly patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (Slapak et al., 1992; Ferrero, et al., 2004). In a prospective study, a combination of active vitamin D and α- interferon has shown to be effective in patients with metastatic renal cell carcinoma (Obara et al., 2008). Calcitriol promotes the anti-proliferative effects of gemcitabine and cisplatin in human bladder cancer models (Ma et al., 2010), and also potentiates antitumor activity of paclitaxel and docetaxel (Hershberger et al., 2001; Ting et al. 2007). A phase II study showed that high-dose calcitriol with docetaxel may increase

time to progression in patients with incurable pancreatic cancer when compared with docetaxel monotherapy (Blanke, 2009).

2. Risk factors for the development of both vitamin D deficiency and cancer

It has been noted that vitamin D and cancer share many of the same risk factors, including both environmental (air pollution, geographic and seasonal) and genetic risk factors.

2.1 Environmental factors

Changes in the environment, such as those caused by air pollution, geographic and seasonal factors, may cause diseases that contribute to the development of both vitamin D deficiency and cancer.

2.1.1 Air pollution factors

Atmospheric pollution has been suggested to be a cause of reduced vitamin D synthesis in the skin. In Australia, some authors demonstrated a large difference in vitamin D synthesis between an urban canyon (urbanized environment with tall building) and a typical suburban area (~2.5 km away from urban area) (Kinley et al., 2010). Increased atmospheric pollution may be related to haze from industrial and vehicle sources and lead to decrease in absorption of ultraviolet-B (UVB) photons, thereby reducing the cutaneous vitamin D synthesis (Mimms, 1996; Hollick, 1995). In another study, some reported that the higher atmospheric pollution, the lower the amount of UVB light reaching ground level (Agarwal et al., 2002). They also showed that children living in areas of high atmospheric pollution are at risk of developing vitamin D deficiency rickets. In a study Belgian postmenopausal women who participated in outdoor activities during the summer, urban inhabitants were reported to have an increased prevalence of vitamin D deficiency compared with rural inhabitants (Manicourt & Devogelaer, 2008). In a cross sectional study, living in a polluted area plays a significant independent role in vitamin D deficiency (Hosseinpanah et al., 2010). Similarly, cancer mortality rates (esophagus, stomach, colon-rectum, liver, lung, breast, and bladder) in 263 counties in all Provinces of China were inversely associated with solar UVB exposure by using the National Central Cancer Registries (NCCR) of China, satellite measurements of cloud-adjusted ambient UVB intensity that were obtained from the NASA Goddard Space Flight Center Data Archive Center database, and the Geographic Information System (GIS) methods (Chen et al., 2010). Cancer incidence rates (esophagus, stomach, colon-rectum, and cervix) in 30 counties were inversely correlated with ambient UVB exposure. Lung cancer mortality has been shown the strongest inverse correlation with an estimated 12% fall per 10 mW/(nm m^2) increase in UVB irradiance even adjusted for smoking. These associations were similar to those observed in a number of populations of European origin.

2.1.2 Geographic factors

The relationship between the geographical variation of colon cancer mortality rates and vitamin D related to UVB was first proposed in 1980 (Garland & Garland, 1980). The authors showed that the colon mortality rates are highest in the Northeast and lowest in the Southwest of the United States from 1950 - 1969 and was correlated to the annual hours of sunshine. It has been observed that with each 10 degrees distance from equator, there is a

progressive decrease in UVB radiation exposure (Diffey, 1991). Solar UVB is the primary source of vitamin D for most people living on Earth. Nuclear submarine crewmen who were not exposed to UVB for 3 months showed a decrease in an already low circulating $25OHD_3$ level from 13.7 to 7.9 ng/ml (Garland & Garland, 1980). Grant determined that 14 types of cancer (bladder, breast, colon, endometrial, esophageal, gallbladder, gastric, ovarian, pancreatic, rectal, renal and vulvar cancer and both Hodgkin's and non-Hodgkin's lymphoma) had mortality rates inversely correlated with solar UVB levels (Grant, 2009). During the cold weather, latitude was found to determine levels of vitamin D-producing UV radiation. As latitude increase, vitamin D producing UV radiation decreases dramatically and may inhibit vitamin D synthesis in humans (Kimlin et al., 2007).

2.1.3 Seasonal factors

Seasonal variations of $25OHD_3$ were reported either in southern and northern latitudes (Oliveri et al., 1993; Stryd et al., 1979). Another study confirmed and quantified the relatively large seasonal fluctuations in circulating $25OHD_3$ levels in association with summer sun exposure among outdoor workers. Their median serum $25OHD_3$ levels decreased from 122 nmol/L in late summer to 74 nmol/L in late winter (Barger-Lux & Heany, 2002). Similarly, a seasonal pattern has been noticed in many cancers with the highest in the winter and springs – including lung cancer, brain tumors, parathyroid tumor, non-Hodgkin's lymphoma, Hodgkin's lymphoma, childhood leukemia/lymphoma, monocytic leukemia, breast cancer, thyroid cancer, bladder carcinoma, and cervical cancer. In the summer and autumn season, certain cancers (breast, colon, prostate, Hodgkin's lymphoma, and lung) have a better survival rates than during other seasons (Luong & Nguyen, 2010).

2.2 Genetic factors

Genetic studies provide an excellent opportunity to link molecular variations with epidemiological data. *DNA* sequences variations such as polymorphisms have modest and subtle biological effects. Receptors play a crucial role in the regulation of cellular function, and small changes in their structure can influence intracellular signal transduction pathways.

The *VDR* is expressed and regulated in mammary gland during the reproductive cycle (Zinser & Welsh, 2004). *VDR* ablation is associated with ductal ectasia of the primary ducts, loss of secondary and tertiary ductal branches and atrophy of the mammary fat pad (Welsh et al., 2011). *VDR* has also been demonstrated to be lowered in human colorectal adenocarcinoma biopsies (34.5%) than in adjacent normal mucosa (82.5%) (Meggouh et al., 1990). In this colorectal adenocarcinoma, the incidence decreased from right colon (64.7%) to left colon (27.7%), and rectum (15%). Certain allelic variations in the *VDR* may also be genetic risk factors for developing tumors. There are five important common polymorphisms within the *VDR* gene region that are likely to exert functional effects on *VDR* expression. *Cdx2*, located in the promoter region of exon 1, affects the binding ability of *VDR* and subsequent *VDR* transcription activity; *Fok*1 located in translation start of the exon 2; and three other variants (*Bsm*1, *Apa*1 and *Taq*1) located at the 3' end of *VDR*s that may influence *VDR* expression by altering the *mRNA* stability. In a review of the literature, an association of *VDR* polymorphisms and cancer prognosis are reported to be strongest for prostate cancer (*Fok*1 and *Taq*1), breast cancer (*Bsm*1, *Taq*1 and *Apa*1), malignant melanoma

(*Bsm*1, *Fok*1 and *Taq*1), renal cell carcinoma (*Taq*1), colorectal cancer (*Apa*1, *Fok*1, *Bsm*1, and *Taq*1), epithelial ovarian cancer (*Fok*1), lung cancer (*Taq*1), and oral squamous cell carcinoma (*Taq*1) (Köstner et al., 2009; Mahmoudi et al., 2010; Slattery et al., 2001; Slattery et al., 2006; Taylor et al., 1996; Lundin et al., 1999; Hutchinson et al., 2000; Tamez et al., 2009; Dogan et al., 2009; Bektas-Kayhan et al., 2010). However, other reports are conflicting and the role of *VDR* polymorphisms remains obscure. Their studies revealed no relationship between prostate and breast cancers and *VDR* variants (Ntais et al., 2003; Császá & Abel, 2001; Newcomb et al., 2002; Buyru et al., 2003).

There are numerous potential gene products that are transcriptionally activated by *p53* and are involved in cell cycle arrest or apoptosis (Ko & Prives, 1996). Some authors demonstrated a trend toward lower risk of a *p53* mutation with increased hours of sunshine exposure (Slattery et al., 2010). They also reported specific point mutations of the *p53* gene were associated with the *Fok*1 and *Cdx2 VDR* genotypes. The *p53* is one of the more commonly mutated genes in rectal and pancreatic tumors (Slattery et al., 2009; Slebos et al., 2000). The mutated *p53* gene increases the nuclear accumulation of *VDR*, even in the absence of added vitamin D, and converts vitamin D into an anti-apoptotic agent (Stambolsky et al., 2010).

The cytochrome P_{450} (*CYP*) is responsible for the oxidation, peroxidation, and/or reduction of vitamins, steroids, xenobiotics, and metabolism of drugs. The *CYP*27*B*1 (25-hydroxyvitamin D_3-1α-hydroxylase) enzyme catalyzes the 1α-hydroxylation of the $25OHD_3$ to $1,25OHD_3$, the most active form of vitamin D_3 metabolite. 1α-hydroxylase is down-regulated early in the neoplastic process of prostatic cancer cells (Chen et al., 2003; Hsu et at., 2001). In another study, the common genotypic variation in *CYP*27*B*1, however, has little or no effect on overall prostate cancer risk (Holt et al., 2009). The *CYP27B1 mRNA* in malignant breast tumors was reported to decrease in comparison with normal mammary tissue (McCarthy et al., 2009). 1α-hydroxylation levels were found elevated in malignant pancreatic cells and their proliferation is inhibited by prohormone $25OHD_3$ (Schwartz et al., 2004). Calcitriol significantly increased the 24-hydroxylase *mRNA* in the human cervical adenocarcinoma and the human ovarian adenocarcinoma cell lines (Kloss et al., 2010). The *CYP24A1* encodes for the catabolic enzyme 24-hydroxylase and is responsible for inactivating vitamin D metabolites. The *CYP24A1 gene* was found to be amplified in breast cancer (Albertson et al., 2000). In prostate cancer mortality, significantly altered risks of recurrence/progression were observed in relation to genotype for two *tagSNPs* (single-nucleotide polymorphisms) of *VDR*, *CYP24A1*, and one *CYP*27*B*1 (Holt et al., 2010); *CYP24A1* expression is inversely correlated with promoter *DNA* methylation in prostate cancer cell lines (Luo et al., 2010), and its overexpression was also observed to be associated with poorer survival in patients with lung adenocarcinoma (Chen et al., 2011). The gene encoding for *CYP24A1* and *CYP*27*B*1 have been observed to be expressed in colon cancer cells (Anderson et al., 2006; Tangpricha et al., 2001). Variants of *CYP24A1* and *CYP*27*B*1 have also been reported to be associated with risk of distal colon cancer (Dong et al., 2009). There is a deregulation of the vitamin D signaling and metabolic pathways in breast cancer (Lopes et al., 2010). The *VDR* was strongly associated with the estrogen receptor positivity in breast carcinomas. *CYP27B1* expression is slightly lower in invasive carcinomas (44.6%) than in benign lesions (55.8%). In contrast, *CYP24A1* expression was augmented in carcinomas (56% in *in situ* and 53.7% in invasive carcinomas) when compared with that in benign lesions (19%). In another study, however, it has found no difference in the expression of the *VDR*,

CYP27B1, and *CYP24A1 mRNA* in breast cancer and non-neoplastic mammary tissue (de Lyra et al., 2006).

Vitamin D binding protein (DBP) is the main transporter of vitamin D in the bloodstream. DBP-macrophage activating factor (DBP-maf) is considered to be deglycosylated DBP in cancer patients causing inability to activate macrophages and a strong inhibitory activity on prostate tumor cells (Rehder et al., 2009; Gregory et al., 2010). DBP-maf acts as a potent anti-angiogenic factor and inhibits tumor growth *in vivo* (Kalkunte et al., 2005). These authors also reported that DBP-maf also inhibited the vascular endothelial growth factor (VEGF) signaling.

3. Role of vitamin D and its analog in cancer

Calcitriol acts mainly via its high affinity receptor *VDR* through a complex network of genomic (transcription and post-transcription), binds to intracellular *VDR*, which subsequently heterodimerizes with another nuclear retinoid X receptor (*RXR*) and non-genomic mechanisms which may indirectly affect gene transcription via the regulation of intracellular signaling pathways that target transcription factors. *VDR* expressed has been detected in a variety of cultured human cell lines. In breast cancer, the protein levels of the *VDR* were elevated in sensitive cell lines upon $1,25OHD_3$ treatment, whereas resistant clones were unable to induce *VDR* (Jensen et al., 2002). The authors suggested that the levels of *VDR* in cancer might serve as a prognostic marker in cancer treatment with $1,25OHD_3$.

Calcitriol is a potent regulator of cell proliferation, differentiation and apoptosis in a variety of cell types. Calcitriol and its analogs induce apoptosis in tumor cells through the activation of a caspase cascade (Guzey et al., 2002; Weitsman et al., 2003). The caspases have been considered the pivotal executioner of all programmed cell death (Hengartner, 2000). However, calcitriol may induce apoptosis in cancer cells through another novel cascade- and *p53*-independent pathway that can be inhibited by *Bcl*-2 (Mathiasen et al., 1999). Calcitriol and its analogs may cause apoptosis in cancer cells directly by increasing intracellular free calcium ([Ca2+]i) (Vandewalle et al., 1995) and indirectly through the activation of a calcium-dependent cysteine protease, *μ-calpain* (Berry et al., 1999; Mathiasen et al., 2002). Furthermore, calcitriol stimulates membrane phospho-inositide breakdown in human colon cancer cell line, causing translocation of protein kinase C to the membrane, and increasing $[Ca^{2+}]_i$ by both releasing calcium stores and promoting calcium influx (Wali et al., 1992). Calcitriol and it analogs are potent inducers of both active and latent forms of transforming grow factor beta (TGFβ), which participates in the regulation of cell growth, phenotype, and differentiation in various tissues (Koli & Keski-Oja, 1995; Laiho & Keski-Oja, 1992).

Calcitriol has been shown to mediate a G_2/M cell cycle progression and induce cell death in a number of cancer cell lines via direct induction of $GADD_{45a}$, which is a *DNA*-induced and *p53*-regulated gene that plays an essential role in cell cycle control and *DNA* repair (Jiang et al., 2003; Akutsu et al., 2001). By contrast, the anti-proliferative functions of *VDR* are associated at the G_0/G_1 stage of the cell cycle, coupled with upregulation of a number of cell cycle inhibitors, kinase inhibitors $p21^{(waf1/cip1)}$ (Saramäki et al., 2006). However, paricalcitol arrested in G_1/G_0 phases and G_2/M phases in leukemia cell lines, in G_1G_0 in myeloma cells, and induced the expression of $p21^{(waf1/cip1)}$ and $p27^{(Kip1)}$, and down –regulation of $p45^{SKP2}$ (Wang et al., 1996; Munker et al., 1996; Jiang et al., 1994; Lin et al., 2003).

Angiogenesis has been suggested as an indicator of neoplastic transformation. Calcitriol has been reported a potent inhibitor of tumor cell-induced angiogenesis (Shokravi et al., 1995; Majewski et al., 1996). Calcitriol inhibits hypoxia inducible factor-1(HIF-1)/VEGF pathway

in human cancer cells (Ben-Shoshan et al., 2007). Increased levels of HIF-1 activity are often associated with increased tumor aggressiveness, therapeutic resistance, and mortality (Semenza, 2003). VEGF stimulates endothelial cells to proliferate, migrate, and organize into capillary beds (Polverini et al., 2002). DBP-maf inhibited VEGF signaling by decreasing VEGF-mediated phosphorylation of VEGFR-2 and ERK1/2, a downstream target of the VEGF signaling cascade (Kalkunte et al., 2005). Calcitriol and its analogs have been demonstrated to inhibit tumor invasion and metastasis by reducing the expression of serine proteinases, metalloproteinases (MMP-2 and MMP-9), VEGF and parathyroid hormone related peptide (*PTHrP*) in lung carcinoma cell lines (LLC-GFP cells) (Nakagawa et al., 2005a). The metastatic growth of LLC-GFP cells was remarkably reduced in response to calcitriol (Nakagawa et al., 2005b).

Calcitriol and its analogs induced the expression of tumor suppressor gene *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) (Liu et al., 2005; Kumagai et al., 2003). Overexpression of *VDR* stimulated the activity of *PTEN* promoter and also enhances the *PTEN* protein level (Pan et al., 2009). The *PTEN* phosphatase can block phosphoinositide 3-kinase/AKT (PI3K/Akt) signaling pathway, which contribute to both cell death and the inhibition of cell proliferation (Cantley & Neel, 1999). *PTEN* mutations have been found in many human cancers (Tamura et al., 1999). In colon cancer cells, calcitriol and its analogs increase the expression of *E-cadherin*, a transmembrane protein located in intercellular adherent junctions, which make cells more adherent to each other (Pálmer et al., 2001). Loss of *E-cadherin* expression is a common even during the transition from adenoma to carcinoma (Perl et al., 1998). *E-cadherin* is a tumor suppressor gene, and its decrease in expression is associated with poor prognosis in patients with prostate cancer (Umbas et al., 1994). Vitamin D also suppresses *tenascin-C*, which promotes growth, invasion, and angiogenesis during tumorigenesis (Gonzàlez-Sancho et al., 1998).

The induction of ornithine decarboxylase (ODC) may be an essential process in the mechanism of tumor promotion (O'brien et al., 1975), and calcitriol has been reported to inhibit tumor promoter-induced ODC expression in the skin, stomach, colon, and liver in animals (Hashiba et al., 1987). Calcitriol, however, did not induce epidermal ODC activity, but inhibited the induction of ODC by the tumor promoters 12-0-tetradecanoylphorbol-13-acetate (TPA) and teleocidin, suggesting that it is an anti-promoter rather than a promoter in mouse skin carcinogenesis (Chida et al., 1984).

Calcitriol has been reported to regulate the transcription of the tumor necrosis factor alpha (TNF-α) without affecting translation in leukemia cell line (Steffen et al, 1988), may increase the sensitivity of cancer cells to TNF-α and potentiates the cytotoxic effect of the cytokine (Yacobi et al., 1996), which is an important factor in immunological anti-cancer therapy. TNF-α potentiates the effect of $1,25OHD_3$ in inducing of differentiation of human myeloid cell lines (Trinchieri et al., 1987).

Prostaglandins (PGs) have been shown to play a role in the development and progression of many cancers. Calcitriol has been reported to regulate the expression of several key genes involved in the PG pathway causing a decrease in PG synthesis (Moreno et al., 2005). Cyclooxygenase (COX) participates in the conversion of arachidonic acid to PGs. COX-2 has been reported to increase in various malignancies (van Rees et al., 2001; Ristimaki et al., 2002). Calcitriol and its analogs decreased expression of COX-2 in colon cancer cells (Kumagai et al., 2003). Selective COX-2 inhibitor reduces the polyp in patients with familial adenomatous polyposis (Steinbach et al., 2000). 15-hydroxy-prostaglandin dehydrogenase (15-PGDH) is the enzyme that catalyzes the conversion of PGs to their corresponding 15-

keto derivatives; 15-PGDH has been demonstrated as an oncogene antagonist and plays a tumor-suppressive role in colon cancer (Yan et al., 2004). Calcitriol increases 15-PGDH *mRNA* and protein expression in various prostate cancer cells (Moreno et al., 2005). Calcitriol has also found to regulate COX-2 and 15-PGDH expression in other cells (Pichaud et al., 1997; Aparna et al., 2008). Calcitriol and its analogs can significantly decrease intestinal tumor load in Apc^{Min} mice (Huerta et al., 2002). Vitamin D and its metabolites have been known to inhibit cell proliferation in human rectal mucosa and a colon cancer cell line (Thomas et al., 1992).

The human peroxisome proliferator-activated receptor delta (*PPARδ*) and *VDR* signaling pathways regulate a multiple of genes that are of importance for a multiple of cellular functions including cell proliferation, cell differentiation, immune response and apoptosis. The provided link between *VDR* and *PPAR* may play an important role in treatment in prostate cancer and melanoma (Peehl & Feldman, 2004; Sertznig et al., 2009). *PPARδ* expression was reported to be increased by 1.5–3.2-fold after a 3-h stimulation of breast and prostate cancer cell lines with $1,25OHD_3$ (Dunlop et al., 2005). *PPARδ* has been reported to regulate lung cancer cell growth (Fukumoto et al., 2005) and it also may attenuate colon and skin carcinogenesis (Hartman et al., 2004; Marin et al., 2006; Kim et al., 2004). In addition, *PPARδ* deficiency does not suppress intestinal tumorigenesis in $Apc^{Min/+}$ mice (Reed et al., 2004).

Hypercalcemia is a common complication of paraneoplastic syndromes and is a contributor to the morbidity of cancer patients; in most cases, hypercalcemia is mediated by *PHTrP*. The *PTHrP* production has been suppressed by $1,25OHD_3$ and its analogs in cancer cell line via down-regulation and suppression of epidermal growth factor (ECF)-induced *PTHrP* gene expression (Kremer et al., 1996; Kunakornsawat et al., 2002; Fazon et al., 1998). Calcitonin has been known to secrete in response to high calcium level and C cell of the human medullary carcinoma and was suppressed by calcitriol (Telenius-Berg et al., 1975; Zabel & Dietel, 1991).

4. Conclusion

Vitamin D certainly has a role in the prevention and treatment of cancer. It is necessary to check serum $25OHD_3$ and parathyroid hormone (PTH) status in cancer patients. Serum levels of PTH have been reported to correlate with PSA levels and colorectal cancer (Skinner & Schwartz, 2009; Charalampopoulos et al., 2010). Some authors proposed that, in patients with normal calcium levels, the serum $25OHD_3$ levels should be stored to > 55ng/ml in cancer patients (colon, breast, and ovary) (Garland et al., 2007). Calcitriol, $1,25OHD_3$, is best used for cancer treatment, because of its active form of vitamin D_3 metabolite, suppression of PTH levels (acted as cellular growth factor), and their receptors presented in most of human cells. However, monitor of serum $25OHD_3$ after taking calcitriol is not necessary because calcitriol inhibits the production of serum $25OHD_3$ by the liver (Bell et al., 1984; Luong & Nguyen, 1996). The main limitation to the clinical widespread evolution of $1,25OHD_3$ is its hypercalcemic side-effects.

5. References

Agarwal, KS; Mughal, MZ; Upadhyay, P; et al. (2002). The impact of atmostpheric pollution on vitamin D status of infants and toddlers in Delhi, India. *Arch Dis Child.* Vol.87, pp.111-113.

Anderson, MG; Nakane, M; Ruan, X; et al. (2003). Expression of VDR and CYP24A1 mRNA in human tumors. *Cancer Chemother Pharmacol.* Vol.57, pp.234-240.

Albertson, DG; Ylstra, B; Segraves, B; et al. (2000). Quantitative mapping of amplicon structure by array CHG identifies CYP24 as a candidate oncogene. *Nat Genet.* Vol.25, pp.144-146.

Aparna, R; Subhashini, J; Roy, KR; et al. (2008). Selective inhibition of cyclooxygenase-2 (COX-2) by 1alpha-,25-dihydroxy-16-ene-23-yne-vitamin D_3, a less calcemic vitamin D analog. *J Cell Biochem.* Vol.104, pp.1832-1842.

Autier, P and Gandini, S (2007).Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med.* Vol.167, pp.1730-1737.

Barger-Lux, MJ; Heany, RP. (2002). Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. *J Clin Endocrinol Metab.* Vol.87, pp.4952-4956.

Beer, TM; Lemmon, D; Lowe, BA; et al. (2003). High-dose weekly oral calcitriol in patients with a rising PSA after prostatectomy or radiation for prostate carcinoma. *Cancer.* Vol.97, pp.1217-1224.

Beer, TM; Venner, PM; Ryan, CW; et al. (2006). High dose calcitriol may reduce thrombosis in cancer patients. *Br J Hematol.* Vol.135, pp.392-394.

Bektas-Kayhan, K; Unür, M; Yaylim-Eraltan, I; et al. (2010). Association of vitamin D receptor Taq1 polymorphism and susceptibility to oral squamous cell carcinoma. *In Vivo.* Vol.24, No.5, pp.755-759.

Ben-Shoshan , M; Amir, S; Dang, DT; et al. (2011). 1α,25-dihydroxyvitamin D_3 (calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells. *Mol Cancer Ther.* Vol.6, No.4, pp.1433-1439.

Bell, NH; Shaw, S; and Turner, RT. (1984). Evidence that 1,25-dihydroxyvitamin D_3 inhibits the hepatic production of 25-hydroxyvitamin D in man. *J Clin Invest.* Vol.74, pp.1540-1544.

Berry, DM and Meckling-Gill, KA. (1999). Vitamin D analogs, 20-epi-22-oxa-24a,26a,27a-trihomo-1α,25$(OH)_2$-vitamin D_3, 1,24$(OH)_2$-22-ene-24-cyclopropyl-vitamin D_3 and 1α,25$(OH)_2$-lumisterol$_3$ prime NB4 leukemia cells for monocytic differentiation via nongenomic signaling pathways, involving calcium and calpain. *Endocrinology.* Vol.140, pp.4779-4488.

Blanke, CD; Beer, TM; Todd; et al. (2009). Phase II study of calcitriol-enhanced docetaxel in patients with previously untreated metastatic or locally advanced pancreatic cancer. *Investigational New Drugs.* Vol. 27, No.4, pp.374-378.

Bower, M; Colston, KW; Stein, RC; et al. (1991). Topical calcipotriol treatment in advanced breast cancer. *Lancet.* Vol.337, No.8743, pp.701-702.

Buyru, N; Tezol, A; Yosonkaya-Fenerci, E; Dalay, N. (2003). Vitamin D receptor gene polymorphisms in breast cancer. *Exp Mol Med.* Vol.35, pp.550-555.

Cantley, LC and Neel, BG. (1999). New insights into tumor suppression: PTEN suppresses tumor formation by restraining the phosphinositide 3-kinase/AKT pathway. *Proc Natl Acad Sci USA.* Vol.96, pp.4240-4245.

Charalampopoulos, A; Charalabopoulos, A; Batistatou, A; et al. (2010). Parathormone and 1,25$(OH)_2D_3$ but not 25$(OH)D_3$ serum levels, in an inverse correlation, reveal an association with advanced stages of colorectal cancer. *Clin Exp Med.* Vol.10, pp.69-72.

Chen, TC; Wang, L; Whitlatch, LW; et al. (2003). Prostatic 25-hydroxyvitamin D-1alpha-hydroxylase and its implication in prostate cancer. *J Cell Biochem.* Vol.88, pp.315-322.

Chen, W; Clements, M; Rahman, B; et al. (2010). Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China. *Cancer Causes Control.* Vol.21, No.10, pp.1701-1709.

Chen, G; Kim, SH; King, AN; et al. (2011). CYP24A1 is an independent prognostic marker of survival in patients with lung adenocarcinoma. *Clin Cancer Res.* Vol.17, No.4, pp.817-826.

Chida, K; Hashiba, H; Suda, T; et al. (1984). Inhibition by 1α,25-dihydroxyvitamin D_3 of induction of epidermal ornithine decarboxylase caused by 12-0-tetradecanoylphorbol-13-acetate and teleocidin B. *Cancer Res.* Vol.44, pp.1387-1391.

Császá, A and Abel, T. (2001). Receptor polymorphisms and diseases. *Eur J Pharmacol.* Vol.414, pp.9-22.

de Lyra, EC; da Silva, IA; Katayama, ML; et al. (2006). 25$(OH)_2D_3$ serum concentration and breast tissue expression of 1alpha-hydroxylase, 24-hydroxylase and vitamin D receptor in women with and without breast cancer. *J Steroid Biochem Mol Biol.* Vol.100, No.4-5, pp.184-192.

Dalhoff, K; Dancey, J; Astrup, L; et al. (2003). A phase II study of the vitamin D analogue Seocalcitol in patients with inoperable hepatocellular carcinoma. *Br J Cancer.* Vol.89, pp252-257.

Diffey, BL. (1991). Solar ultraviolet radiation effects on biologic systems. *Phys Med Biol.* Vol.36, pp.299-328.

Dogan, I; Onen, HI; Yurdakul, AS; et al. (2009). Polymorphisms in the vitamin D receptor gene and risk of lung cancer. *Med Sci Monit.* Vol.15, No.8, pp.BR232-242.

Dong, LM; Ulrich, CM; Hsu, L; et al. (2009). Vitamin D related genes, *CYP24A1* and *CYP27B1*, and colon cancer risk. *Cancer Epidemiol Biomakers Prev.* Vol.18, No.9, pp.2540-2548.

Dunlop, TW; Väisänen, S; Frank, C; et al. The peroxisome proliferator-activated receptor delta gene is a primary target of 1α,25-dihydroxyvitamin D_3 and its nuclear receptor. *J Mol Biol.* Vol.349, pp.248-260.

Falzon, M; and Zong, J. (1998). The noncalcemic vitamin D analogs EB 1089 and 22-oxacalcitriol suppress serum-induced parathyroid hormone-related peptide gene expression in a lung cancer cell line. *Endocrinology.* Vol.139, pp.1046-1053.

Ferrero, D; Campa, E; Dellacasa, C; et al. (2004). Differentiating agents + low-dose chemotherapy in the management of old/poor prognosis patients with acute myeloid leukemia or myelodysplastic syndrome. *Haematologica.* Vol.89, pp.619-620.

Fukumoto, K; Yano, Y; Virgona, N; et al. (2005). Peroxisome proliferator-activated receptor delta as a molecular target to regulate lung cancer cell growth. *FEBS Lett.* Vol.579, pp.3829-3836.

Garland, CF and Garland, FC. (1980). Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol.* Vol.9, pp.227-231.

Garland, CF; Grant, WB; Mohr, SB; et al. (2007). What is the dose-response relationship between vitamin D and cancer risk? *Nutr Rev.* Vol.65, No.8, Pt.2, pp.S91-S95

Giovannucci, E; Liu, Y; Rimm, EB; et al. (2008). Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst.* Vol.98, pp.451-459.

Gonzàlez-Sancho, JM; Alvarez-Dolado, M; Muñoz, A. (1998). 1,15-dihydroxyvitamin D_3 inhibits tenascin-C expression in mammary epithelial cells. *FEBS Lett.* Vol.426, pp.225-228.

Grant,WB. ((2009). How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer. *Dermato-Endocrinology.* Vol.1, No.1, pp.17-24.

Gregory, KJ; Zhao, B; Bielenberg, DR; et al. (2010). Vitamin D binding protein-macrophage activating factor directly inhibits proliferation, migration, and uPAR expression of prostate cancer cells. *PLos One.* Vol.5, No.10, p.213428.

Guzey, M; Kitada, S; Reed, JC; et al. (2002). Apoptosis induction by 1alpha,25-dihydroxyvitamin D_3 in prostate cancer. *Mol Cancer Ther.* Vol.1, pp.667-677.

Hartman, FS; Nicol, CJ; Marin, HE; et al. (2004). Peroxisome proliferator-activated receptor delta attenuates colon carcinogenesis. *Nat Med.* Vol.10, pp.481-483.

Hashiba, H; Fukushima, M; Chida, K; et al. (1987). Systemic inhibition of tumor promoter-induced ornithine decarboxylase in 1α,25-dihydroxyvitamin D_3-treated animals. *Cancer Res.* Vol.47, pp.5031-5035.

Hengartner, MO. (2000). The biochemistry of apoptosis. *Nature.* Vol.407, pp.770-776.

Hershberger, PA; Yu, WD; Modzelewski, RA; et al. (2001). Calcitriol (1,25-dihydroxycholecalciferol) enhances paclitaxel antitumor activity in vitro and in vivo and accelerates paclitaxel-induced apoptosis. *Clin Cancer Res.* Vol.7, pp.1043-1051.

Hollick, MF. (1995), Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr.* Vol.61(suppl), pp.638S-645S.

Holt, SK; Kwon, EM; Peters, U; et al. (2009). Vitamin D pathway gene variants and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev.* Vol.18, No.6, pp.1928-1933.

Holt, SK; Kwon, EM; Koopmeiners, JS; et al. (2010). Viamin D pathway gene variants and prostate cancer prognosis. *Prostate.* Vol.70, No.13, pp.1448-1460.

Hosseinpanah, F; Hashemi pour, S; Heibatollahi. M; et al. (2010). The effects of air pollution on vitamin D status in healthy women: A cross section study. *BMC Pub Health.* Vol.10, p.519.

Hsu, JY; Feldman, D; McNeal, JE; et al. (2001). Reduced 1alpha-hydroxylase activity in human prostate cancer cells correlates with decreased susceptibility to 25-hroxyvitamin D_3-induced growth inhibition. *Cancer Research.* Vol.61, pp.2852-2856.

Huerta, S; Irwin, RW; Heber, D; et al. (2002). 1alpha,25$(OH)_2$-D_3 and its synthetic analogue decrease tumor load in the Apc^{min} mouse. *Cancer Res.* Vol.62, No.1, pp.741-746.

Hutchinson, PE; Osborne, JE; Lear, JT; et al. (2000). Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. *Clin Cancer Res.* Vol.6, pp.498-504.

Jiang, H; Lin, J, Su, ZZ; et al. (1994). Induction of differentiation in human promyelotic HL-60 leukemia cells activates p21, WAF1/CIP1, expression in the absence of p53. *Oncogene.* Vol.9, pp.3397-3406.

Jensen, SS; Madsen, MW; Lucas, J; et al. (2002). Sensitivity to growth suppression by 1alpha,25-dihydroxyvitamin D_3 among MCF clones correlates with vitamin D receptor protein induction. (2002). *J Steroid Biochem Mol Biol.* Vol.81, pp.123-133.

Kalkunte, S; Brard, L; Granai, CO; Swamy, N. (2005). Inhibition of angiogenesis by vitamin-D binding protein: characterization of anti-endothelial activity of DBP-maf. *Angiogenesis.* Vol.8, pp.349-360.

Kim, DJ; Akiyama, TE; Hartman, FS; et al. (2004). Peroxisome proliferator-activated receptor beta (delta)-dependent regulation of ubiquitin C expression contributes to attenuation of skin carcinogenesis. *J Biol Chem.* Vol.279, pp.23719-23727.

Kimlin, MG; Olds, WJ; Moore, MR. (2007). Location and vitamin D synthesis: is the hypothesis validated by geographical data? *J Phochem Photobiol B.* Vol.86, pp.234-239.

Kinley, AM; Janda, M; Auster, J; Kimlin, M. (2010). In vitro model of vitamin D synthesis by UV radiation in an Australian urban environment. *Photochem Photobiol.* First published online: 2010 Dec 22. DOI: 10.1111/j.1751-1097.2010.00865.x

Kloss, M; Fischer, D; Thill, M; et al. (2010). Vitamin D, calcidiol and calcitriol regulate vitamin D metabolizing enzymes in cervical and ovarian cancer cells. *Anticancer Res.* Vol.30, No.11, pp.4429-4434.

Ko, LJ and Prives, C. (1996). p53: puzzle and paradigm. *Genes Dev.* Vol.10, pp.1054-1072.

Koli, K and Keski-Oja, J. (1995). 1,25-dihroxyvitamin D_3 enhances the expression of transforming growth factor β1 and its latent form binding protein in cultured breast carcinoma cells. *Cancer Res.* Vol.55, pp.1540-1546.

Köstner, K; Denzer, N; Müller, CS; et al (2009). The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. *Anticancer Res.* Vol.29, No.9, pp.3511-3536.

Kremer, R; Shustik, C; Tabak, T; et al. (1996). Parathyroid-hormone-related peptide in hematologis malignancies. *Am J Med.* Vol.100, No.4, pp.406-411.

Kumagai, T; O'Kelly, J; Said, JW; et al. (2003). Vitamin D_2 analog 19-nor-1,25-dihroxyvitamin D_2: antitumor activity against leukemia, myeloma, and colon cancer cells. *J Natl Cancer Inst.* Vol.95, No.12, pp.896-905.

Kunakornsawat, S; Rosol, TJ; Capen, CC; et al. (2002). Effects of 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] and its analogs (EB1089 and analog V) on canine adenocarcinoma (CAC-8) in nude mice. *Biol Pharm Bull.* Vol.25, pp.642-647.

Ma, Y; Yu, WD; Trump, DL; et al. (2010). Enhances antitumor activity of gemcitabine and cisplatin in human bladder cancer models. *Cancer.* Vol.116, pp.3294-3303.

Mahmoudi, T; Mohebbi, SR; Pourhoseingholi, MA; et al. (2010). Vitamin D receptor gene Apa1 polymorphism is associated with susceptibility to colorectal cancer. *Dig Dis Sci.* Vol.55, No.7, pp.2008-2013.

Majewski, S; Skopinska, M; Marczak, M; et al. (1996). Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis. *J Invest Dermatol Symp Proc.* Vol.1, No.1, pp.97-101.

Manicourt, DH and Devogelaer, JP. (2008). Urban tropospheric ozone increases the prevalence of vitamin D deficiency among Belgian postmenopausal women with outdoor activities during summer. *J Clin Endocrinol Metab.* Vol.93, pp.3893-3899.

Marin, HE; Peraza, MA; Billin, AN; et al. (2006). Ligand activation peroxisome proliferator-activated receptor delta inhibits colon carcinogenesis. *Cancer Res.* Vol.66, pp.4394-4401.

Mathiasen, IS; Lademann, U; Jäättelä, M. (1999). Apoptosis induced by vitamin D compounds in breast cancer cells is inhibited by Bcl-2 but does not involve known caspases or p53. *Cancer Res.* Vol.59, pp.4848-4856.

Mathiasen, IS; Sergeev, IN; Bastholm, L; et al. (2002). Cacium and caplain as key mediators of apoptosis-like death induced by vitamin D compounds in creast cancer cells. *J Biol Chem.* Vol.277, pp.30738-30745.

McCarthy, K; Laban, C; Bustin, SA; et al. (2009). Expression 25-hydroxyvitamin D_3-1α-hydroxylase, and vitamin D receptor mRNA in normal and malignant breast tissue. *Anticancer Res.* Vol.29, No.1, pp.155-157.

Meggouh, F; Lointier, P; Pezet, D; Saez, S. (1990). Evidence of 1,25-dihydroxyvitamin D_3 in human digestive mucosa and carcinoma tissue biopsies taken at different levels of the digestive tract, in 152 patients. *J Steroid Biochem.* Vol.36, No.1-2, pp.143-147.

Mims, FM 3rd. (1996). Significant reduction of UVB caused by smoke from biomass burning in Brazil. *Photochem Photobiol.* Vol.64, pp.814-816.

Moreno, J; Krishnan, AV; Swami, S; et al. (2005). Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. *Cancer Res.* Vol.65, pp.7917-7925.

Morris, DL; Jourdan, JL; Finlay, I; et al. (2002). Hepatic intra-arterial injection of 1,25-dihydroxyvitamin D_3 in lipiodol: pilot study in patients with hepatocellular carcinoma. *Int J Oncol.* Vol.21, pp.901-906.

Munker, R; Kobayashi, T; Elstner, E; et al. (1996). A new series of vitamin D analogs is highly active for clonal inhibition, differentiation, and induction of WAF1 in myeloid leukemia. *Blood.* Vol.88, pp.2201-2209.

Nakagawa, K; Sasaki, Y; Kato, S; et al. (2005a). 22-Oxa-1alpha-25-dihydroxyvitamin D_3 inhibits metastasis and angiogenesis in lung cancer. *Carcinogenesis.* Vol.26, pp.1044-1054.

Nakagawa, K; Kawaura, A; Sato, S; et al. (2005b). 1 alpha,25dihydroxyvitamin D_3 is a preventive factor in the metastasis of lung cancer. *Carcinogenesis.* Vol.26, pp. 294-440.

Newcomb, PA;Kim, H;Trentham-Dietz, A; et al. (2002). Vitamin D receptor polymorphism and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* Vol.11, pp.1503-1504.

Ntais, C; Polycarpou, A; Ioannidis, JP. (2003). Vitamin D receptor gene polymorphisms and risk of prostate cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* Vol.12, pp.1395-1402.

Laiho, M and Keski-Oja, J. (1992). Transforming growth factor-β: as regulators of cellular growth and phenotype. *CRC Crit Rev Oncogenesis.* Vol.3, pp.1-26.

Lin, R; Wang, TT; Miller, WH; et al. (2003). Inhibition of F-Box protein $p45^{SKP2}$ expression and stabilization of cyclin-dependent kinase inhibitor $p27^{KIP1}$ in vitamin D analog-treated cancer cells. *Endocrinology.* Vol.144, pp.749-753.

Liu, W; Asa, SL; Ezzat, S. (2005). 1α,25-dihydroxyvitamin D_3 target PTEN-dependent fibronectin expression to restore thyroid cancer cell adhesiveness. *Mol Endocrinol.* Vol.19, pp.2349-2357.

Liu, G; Hu, X; Chakrabarty, S; et al. (2010). Vitamin D mediates its action in human colon carcinoma cells in a calcium-sensing receptor-dependent manner: downregulates malignant cell behavior and the expression of thymidylate synthase and surviving and promotes cellular sensitivity to 5-FU. *Int J Cancer.* Vol.126, pp.631-639.

Lopes, N; Sousa, B; Martins, D; et al. (2010). Alterations in vitamin D signaling and metabolic pathways in breast cancer progression: a study of VDR, CYP27B1 and CYP24A1 expression in benign and malignant breast lesions vitamin D pathways unbalanced in breast lesions. *BMC Cancer.* Vol.10, p.483.

Lundin, AC; Söderkvist, P; Erichsson, B; et al. (1999). Association of breast cancer progression with a vitamin D receptor gene polymorphism. *Cancer Res.* Vol.59, pp.2332-2334.

Luo, WJ; Chen, JY; Xu, W; et al. (2004). Effects of vitamin D analogue EB1089 on proliferation and apoptosis of hepatic carcinoma cells. *Zhonghua Yu Fang Yi Xue Za Zhi.* Vol.38, pp.415-418. [article in Chinese]

Luo, W; Karpf, AR; Deeb, KK; et al. (2010). Epigenetic regulation of vitamin D 24-hydroxylase/CYP24A1 in human prostate cancer. *Cancer Res.* Vol.70, No.14, pp.5953-5962.

Luong, VQK and Nguyen, THL. (1996). Coexisting hyperparathyroidism and primary hyperparathyroidism with vitamin D-deficient osteomalacia in a Vietnamese immigrant. *Endocrine Practice.* Vol.2, pp.250-254.

Luong, VQK and Nguyen, THL. (2010). The beneficial role of vitamin D and its analogs in cancer treatment and prevention. *Crit Rev Oncology/Hematology.* Vol.73, pp.192-201.

O'Brien, TG; Simsiman, RC; Boutwell, RK. (1975). Induction of the polyamine-biosynthetic enzymes in mouse epidermis and their specificity for tumor promotion. *Cancer Res.* Vol.35, pp.2426-2433.

Obara, W; Mizutani, Y; Oyama, C; et al. (2008). Prospective study of combined treatment with interferon-alpha and active vitamin D_3 for Japanese patients with metastatic renal cell carcinoma. *Int J Urol.* Vol.15, No.9, pp.794-799.

Oliveri, MB; Ladizesky, M; Mautalen, CA; et al. (1993). Seasonal variations of 25-hydroxyvitamin D and parathyroid hormone in Ushuala (Argentina), the southernmost city of the world. *Bone Miner.* Vol.20, pp.99-108.

Pálmer, HG; González-Sancho, JM; Espada, J; et al. (2001). Vitamin D_3 promotes the differentiation of colon carcinoma cells by the induction of *E-cadherin* and the inhibition of β-catenin signaling. *J Cell Biol.* Vol.154, No.2, pp.369-387.

Palmieri-Sevier, A; Palmieri, GM; Baumgartner, CJ; Britt, LG. (1993). Case report: long-term remission of parathyroid cancer: possible relation to vitamin D and calcitriol therapy. *Am J Med Sci.* Vol.306, No.5, pp.309-312.

Perl, AK; Wilgenbus, P; Dahl, U; et al. (1998). A causal role for *E-cadherin* in the transition from adenoma to carcinoma. *Nature.* Vol.392, pp.190-193.

Pichaud, F; Roux, S; Frendo, JL; et al. (1997). 1alpha,25-dihydroxyvitamin D_3 induces NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase in human neotal monocytes. *Blood.* Vol.89, pp.2105-2112.

Pilz, S; Dobnig, H; Winklhofer-Roob, B; et al. (2008). Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. *Cancer Epidemiol Biomarkers Prev.* Vol.17, pp.1228-1233.

Polverini, PJ. (2002). Angiogenesis in health and disease: insights into basic mechanisms and therapeutic opportunities. *J Dent Educ.* Vol.66, pp.962-975.

Raina, V; Cunninham, D; Gilchrist, N; Soukop, M. (1991). Alphacalvidol is a nontoxic, effective treatment of follicular small-cleaved cell lymphoma. *Br J Cancer.* Vol.63, pp.463-465.

Reed, KR; Sansom, OJ; Hayes, AJ; et al. (2004). PPARdelta status and Apc-mediated tumorigenesis in the mouse intestine. *Oncogene.* Vol.23, pp.8992-8996.

Rehder, DS; Nelson, RW; Borges, CR. (2009). Glycosylation status of vitamin D binding protein in cancer patients. *Protein Science.* Vol.18, No.10, pp.2036-2042.

Ristimaki, A; Sivula, A; Lundin, J; et al. (2002). Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. *Cancer Res.* Vol.62, pp.632-635.

Saramäki, A; Banwell, CM; Campbell, MJ; Carlberg, C. (2006). Regulation of the human *p21*$^{(waf1/cip1)}$ gene promoter via multiple binding sites for p53 and the D_3 receptor. *Nucleic Acids Res.* Vol.34, pp.543-554.

Schwartz, GG; Eads, D; Rao, A; et al. (2004). Pancreatic cancer cells express 25-hydroxyvitamin D-1α-hydroxylase and their proliferation is inhibited by the prohormone 25-hydroxyvitamin D_3. *Carcinogenesis.* Vol.25, No.6, pp.1015-1026.

Semenza, GL. (2003). Targeting HIF-1 for cancer therapy. *Nat Rev Cancer.* Vol.3, pp.721-732.

Shokravi, MT; Marcus, DM; Alroy, J; et al. (1995). Vitamin D inhibits angiogenesis in transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci.* Vol.36, pp.83-87.

Skinner, HG, and Schwartz, GG. (2009). The relation of serum parathyroid hormone and serum calcium to serum levels of Prostatic-specific antigen: a population-based study. *Cancer Epidemiol Biomarkers Prev.* Vol.18, No.11, pp.2869-2873.

Slapek, CA; Desforges, JF; Fogaren, T; et al. (1992).Treatment of acute myeloid leukemia in the elderly with low-dose cytarabine, hydroxyurea, and calcitriol. *Am J Hematol.* Vol.41, pp.178-183.

Slattery, ML; Yakumo, K; Hoffman, M; Neuhausen, S. (2001). Variants of the VDR gene and risk of colon cancer (United States). *Cancer Causes Control.* Vol.12, No.4, pp.359-364.

Slattery, ML; Sweeney, C; Murtaugh, M; et al. (2006). Associations between vitamin D, vitamin D receptor gene and the and the androgen receptor gene with colon and rectal cancer. *Int J Cancer.* Vol.118, No.12, pp.3140-3146.

Slattery, ML; Curtin, K; Wolff, RK; et al. (2009). A compromise of colon and rectal somatic DNA alterations. *Dis Colon Rectum.* Vol.52, pp.1304-1311.

Slattery, ML; Wolff, RK; Herrick, JS; et al. (2010). Calcium, vitamin D, VDR genotypes, and epigenetic changes in rectal tumors. *Nutr Cancer.* Vol.62, No.4, pp.436-442.

Slebos, RJC; Hoppin, JA; Tolbert, PE; et al. (2000). K-ras and p53 in pancreatic cancer: association with medical history, histopathology, and environmental exposures in a population-based study. *Cancer Epidemiol Biomarkers Prev.* Vol.9, N0.11, pp.1223-1232.

Stambolsky, P; Tabach, Y; Fontemaggi, G; et al. (2010). Modulation of the vitamin D_3 response by cancer-associated mutant p53. *Cancer Cell.* Vol.17, No.3, pp.273-285.

Steinbach, G; Lynch, PM; Phillips, RK; et al. (2000). The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med.* Vol.342, pp.1946-1952.

Steffen, M; Cayre, Y; Manogue, KR; et al. (1988). 1,25-dihydroxyvitamin D_3 transcriptionally regulates tumour necrosis factor mRNA during HL-60 cell differentiation. *Immunology.* Vol.63, pp.43-46.

Stryd, RP; Gilbertson, TJ; Bruden, MN. (1979). A seasonal variation study of 25-hydroxyvitamin D_3 serum levels in normal human. *J Clin Endocrinol Metab.* Vol.48, pp.771-775.

Tamez, S; Norizoe, C; Ochiai, K; et al. (2009). Vitamin D receptor polymorphisms and prognosis of patients with epithelial ovarian cancer. *Br J Cancer.* Vol.101, pp.1957-1960.

Tangpricha, V; Flanagan, JN; Whitlatch, LW; et al. (2001). 25-hydroxyvitamin D_3-1α-hydroxylase in normal and malignant colon tissue. *Lancet.* Vol.357, pp.1673-1674.

Taylor, JA; Hirvonen, A; Watson, M; et al. (1996). Association of prostate cancer with vitamin D receptor gene polymorphisms. *Cancer Res.* Vol.56, pp.4108-4110.

Telenius-Berg, M; Almqvist, S; Wästhed, B. (1975). Serum calcitonin response to induce hypercalcemia. *Acta Med Scand.* Vol.197, No.5, pp.367-375.

Thomas, MG; Tebbutt, S; Williamson, RC. (1992). Vitamin D and its metabolites inhibit cell proliferation in human rectal mucosa and a colon cancer cell line. *Gut.* Vol.33, No.12, pp.1660-1663.

Ting, HJ; Hsu, J; Bao,BY; Lee, YF. (2007). Docetaxel-induced growth inhibition an apoptosis in androgen indepenpent prostate cancer cells are enhanced by 1alpha,25-dihydroxyvitamin D_3. *Cancer Lett.* Vol.247, pp.122-129.

Trinchierie, G; Rosen, M; Perussia, B. (1987). Induction of differentiation of human myeloid cell lines by tumor necrosis factor in cooperation with 1alpha,25-dihydroxyvitamin D_3. *Cancer Res.* Vol.47, pp.2236-2242.

Tumura, M; Gu, J; Tran, H; Yamada, KM. (1999). PTEN gene and integrin signaling in cancer. *J Natl Cancer Inst.* Vol.91, pp.1820-1828.

Umbas, R; Isaacs, WB; Bringuier, PP; et al. (1994). Decreased *E-cadherin* expression is associated with poor prognosis in patients with prostate cancer. *Cancer Res.* Vol.54, pp.3939-3933.

Wang, QM; Jones, JP; Studzinski, GP. (1996). Cyclin-dependent kinase inhibitor p27 as a mediator of the G1-S phase block induced by 1,25-dihydroxyvitamin D_3 in HL60 cells. *Cancer Res.* Vol.56, pp.264-267.

Wali, RK; Baum, CL; Bolt, MJ; et al. (1992). 1,25-dihydroxyvitamin D_3 inhibits Na^+-H^+ exchange by stimulating membrane phosphoinositide turnover and increasing cytosolic calcium in CaC0-2 cells. *Endocrinology.* Vol.131, No.3, pp.1125-1133.

Weitsman, GE; Ravid, A; Liberman, UA; et al. (2003). Vitamin D enhances caspase-dependent and independent TNF-induced breast cancer cell death: the role of reactive oxygen species. *Ann N Y Acad Sci.* Vol.1010, pp.437-440.

Welsh, JE; Zinser, LN; Mianecki-Morton, L; et al. (2011). Age-related changes in the epithelial and stromal compartments of the mammary gland in normocalcemic mice lacking the vitamin D_3 receptor. *PLoS One.* Vol.6, No.1, p.e16479.

Yacobi, R; Koren, R; Liberman, UA; et al. (1996). 1alpha,25-dihydroxyvitamin D_3 increases the sensitivity of human renal carcinoma cells to tumor necrosis factor alpha but not to interferon alpha or lymphokine-activated killer cells. *J Endocrinol.* Vol.149, pp.327-333.

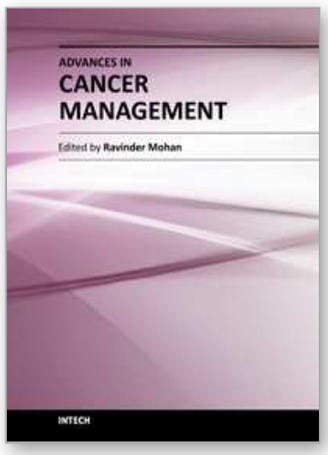
Zabel, M and Dietel, M. (1991). Calcitriol decreases calcitonin secretion from a human medullary carcinoma cell line via specific receptor action. *Acta Endocrinol (Copenh).* Vol.125, No.3, pp.299-304.

Yan, M; Rerko, RM; Platzer, P; et al. (2004). 15-hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-beta-induced suppressor of human gastrointestinal cancer. *PNAS.* Vol.101, pp.17468-17473.

Zinser, GM and Welsh, JE. (2004). Accelerated mammary gland development during pregnancy and delayed postlactational involution in vitamin D_3 receptor null mice. *Mol Endocrinol.* Vol.18, pp.2208-2223.

van Rees, BP and Ristimaki, A. (2001). Cyclooxygenase-2 in carcinogenesis of the gastrointestinal tract. *Scand J Gastrenterol.* Vol.36, pp.897-903.

Vandevalle, B; Hornez, L; Wattez, N; et al. (1995). Vitamin-D_3 derivatives and breast-tumor cell growth: effect on intracellular calcium and apoptosis. *Int J Cancer.* Vol.61, pp. 806-811.



Advances in Cancer Management

Edited by Prof. Ravinder Mohan

ISBN 978-953-307-870-0
Hard cover, 278 pages
Publisher InTech
Published online 27, January, 2012
Published in print edition January, 2012

Cancer is now the most common cause of death in the world. However, because of early diagnosis, better treatment, and advanced life expectancy, many cancer patients frequently live a long, happy, and healthy life after the diagnosis- and often live as long as patients who eventually do not die because of cancer. This book presents newer advances in diagnosis and treatment of specific cancers, an evidence-based and realistic approach to the selection of cancer treatment, and cutting-edge laboratory developments such as the use of the MALDI technique and computational methods that can be used to detect newer protein biomarkers of cancers in diagnosis and to evaluate the success of treatment.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Khanh vinh quốc Lương and Lan Thị Hòang Nguyễn (2012). Vitamin D and Cancer, Advances in Cancer Management, Prof. Ravinder Mohan (Ed.), ISBN: 978-953-307-870-0, InTech, Available from: http://www.intechopen.com/books/advances-in-cancer-management/vitamin-d-cancer

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen